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ORIGINAL RESEARCH

Risk factors of post-operative recurrence and adequate surgical approach to improve long-term outcomes of hepatocellular carcinoma

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Abstract

Introduction: A high recurrence rate of hepatocellular carcinoma (HCC) remains a significant concern. The risk factors for recurrence were analysed and the optimal surgical approaches were investigated.

Methods: The subjects comprised 280 consecutive patients with primary solitary HCC measuring ≤5 cm in diameter, who underwent curative resections. Multivariate analysis was conducted to identify the risk factors for post-operative recurrence, and the clinical significance of an anatomic resection was evaluated.

Results: Multivariate analysis identified HCV infection, a des-gamma-carboxyprothrombin level >100 mAU/ml, underlying cirrhosis, the presence of microvascular invasion, the presence of micrometastases and non-anatomic resection as being significant risk factors for post-operative recurrence. The 5-year recurrence rate was 56.7% in the anatomic resection (AR) group and 74.7% in the non-AR group. The 5-year survival rate was 82.2% in the AR group and 71.9% in the non-AR group. Local recurrence within the same segment was observed in 25% of the patients of the non-AR group. The prognostic superiority of AR was confirmed only in patients with histopathological evidence of microvascular invasion and/or micrometastases, and in patients having a solitary HCC measuring 2 to 5 cm in diameter.

Conclusions: Anatomic resection may decrease local recurrence and improve the surgical outcomes in solitary HCC measuring 2 to 5 cm in diameter.

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Introduction

In spite of the recent improvements in the therapeutic strategies for hepatocellular carcinoma (HCC),[1] the cumulative recurrence rate of HCC remains as high as 50%–60% at 3 years and 70%–100% at 5 years, even after curative liver resection.[2–7]

To date, various factors influencing the risk of recurrence of HCC have been reported, including tumour size,[8–10] tumour number,[8–11] vascular invasion,[8,12–15] the presence of satellite nodules,[16,17] histopathological grade,[11] underlying cirrhosis[16,17] and the type of surgery (i.e. major vs. minor resections, anatomic vs. non-anatomic resections, wide vs. narrow surgical margins, etc.).[4,18–21] Nevertheless, it still remains under debate as to what extent the surgical strategy might contribute to reducing the risk of intrahepatic tumour recurrence.

Recent studies have shown that systematic resection of the tumour-bearing portal territory (anatomic resection) may improve the disease-free survival,[4,18,20,22–26] and even the overall survival,[18,22,25,26] in patients with HCC. The rationale for anatomic resection of the tumour-bearing portal territory is that HCCs tend to spread intrahepatically via portal venous tributaries. However,

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only a few clinicopathological reports are available with regard to the local recurrence rate after anatomic resection[23,25] or the actual distribution of micrometastases around the tumour.[24] The purposes of this study were to revisit the risk factors for intrahepatic tumour recurrence after surgical resection of HCC and to investigate the optimal surgical approach based on the clinicopathological outcomes.

Patients and methods

Study population

The subject pool consisted of 494 consecutive patients who underwent curative liver resection for primary and solitary HCC between January 1994 and December 2008 at the University of Tokyo Hospital. Among these, the patients who were found to have vascular tumour thrombosis on pre-operative imaging (n = 93) or had a history of other malignancy within 5 years prior to the surgery (n = 17) were excluded from the analysis. In addition, to clearly determine the clinical significance of Couinaud's segmentectomy, HCC patients with tumours measuring >5 cm in diameter (n = 104) were also excluded, based on the finding from our prospective database since 1994, that only 14.8% of patients with HCCs exceeding 5 cm in tumour diameter were treatable by Couinaud's segmentectomy, and that the remaining 85.2% required extended resection of 2 or more segments. The remaining 280 patients, consisting of 210 men (75.0%) and 70 women (25.0%), ranging in age from 13 to 85 years (median age, 65), were enrolled in the present analysis.

Surgical treatment

The indication for surgery was based on an algorithm including the presence/absence of ascites, the serum total bilirubin level and the results of the indocyanine green retention test, as previously described.[8,18] Given the fact that HCC has a high propensity to invade the portal veins, and that intrahepatic metastasis via the portal venous tributaries is one of the major mechanisms of recurrence, systematic resection of the tumour-bearing portal regions was performed in the patients, as long as the procedure was permitted by the functional reserve of the liver.[27]

Anatomic resection (AR) was defined as any type of systematic resection of the portal regions based on Couinaud's classification. Technically, the procedure for AR includes the following four steps: (i) confirmation and marking of the segmental border on the liver surface by a segmental staining method[28,29] or by occlusion of the segmental inflow; (ii) parenchymal transection from the segmental border to the landmark veins under ultrasound guidance;[28] (iii) full exposure of the landmark veins on the cut surface of the liver; and (iv) ligation of the segmental portal pedicle near the root of the segment. In this study, only the surgical manoeuvres where all of these four steps were completed were classified as AR. Other surgical manoeuvres, including incomplete removal of the tumour-bearing portal regions, such as wedge resection or enucleation, were classified as a non-anatomic resection (non-AR).

Histopathological classification

The tumour size and width of the surgical margin were recorded before the specimens were fixed. The histological grade of differentiation of the tumour, the degree of fibrosis in the background liver and the presence/absence of vascular invasion were also assessed microscopically based on the classification system proposed by the Liver Cancer Study Group of Japan.[30] A diagnosis of liver cirrhosis was based on histopathological evidence of grade 4 fibrosis according to Desmet's classification.[30,31]

Patient follow-up

All the patients were regularly screened for recurrences through monitoring of the plasma levels of the HCC-specific tumour markers, alpha-fetoprotein (AFP) and des-γ-carboxyprothrombin (DCP), every 1–2 months, ultrasonography every 2 months and dynamic computed tomography every 4 months, as previously reported.[32] Recurrence was defined as the appearance of a new lesion having radiological features compatible with HCC, as confirmed using at least two imaging modalities. When a recurrence was detected, the patient received further treatment by repeat hepatectomy, locoregional ablation therapies including radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE) or other treatment options, as indicated. In the present study, the recurrence-free survival period was defined as the interval between the operation and the date of the diagnosis of the first recurrence (either intrahepatic or extrahepatic). The remaining cases were censored at the date of the last follow-up examination.

Data analysis

Statistical analysis was performed using the IBM SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA). The medians and ranges of continuous data were compared using the Mann–Whitney U-test. Categorical data were compared using Pearson's chi-squared test or Fisher's exact test, as appropriate. P-values of <0.05 were considered to be statistically significant.

Survival curves were generated using the Kaplan–Meier method and compared by the log-rank test. To identify the risk factors for tumour recurrence, a multivariate regression analysis was performed using the Cox proportional hazard model with backward elimination, using variables with $P < 0.20$ in the univariate analysis. All the analyses in this study were performed in accordance with the ethical guidelines for clinical studies at the University of Tokyo Hospital.

Results

Overview

The clinicopathological characteristics of the study population are summarized in Table 1. During the median follow-up period of 57.6 months (range, 1–186.8), 165 patients (58.9%) developed tumour recurrence and 75 patients (26.8%) died. Among the 205 censored cases, 37 patients (18%) were lost to follow-up during the study period. The 1-, 3-, and 5-year survival rates were 98.9%,

Table 1 Patient characteristics (n = 280)

Age, median (range)	65 (13–85)
Gender, male	210 (75.0)
HBsAg positive	59 (21.1)
HCV-Ab positive	174 (62.1)
Child–Pugh	
A	245 (87.5)
B	35 (12.5)
Tumour size (mm), median (range)	28 (8–50)
Types of surgery	
Non-anatomic resection	96 (34.3)
Anatomic resection	184 (65.7)
Segmentectomy	151
Sectorectomy	23
Hemihepatectomy	10
AFP (ng/ml), median (range)	16 (1–37081)
DCP (mAU/ml), median (range)	36 (0–23630)
Macroscopic types[a]	
VN or SN	175 (63.2)
SNEG	65 (23.5)
CM	36 (13.0)
unknown	4 (1.4)
Capsule formation	215 (77.1)
Histological grade	
Well	54 (19.8)
Moderate	194 (71.1)
Poorly/undifferentiated	25 (9.2)
Unknown	7 (2.5)
Microscopic invasion or metastasis	76 (27.1)

Parentheses represent percentage unless indicated.
[a]Classification of Liver Cancer Study Group of Japan.[30]
HBsAg: hepatitis B surface antigen, HCV-Ab: anti-hepatitis C antibody, AFP: alpha-fetoprotein, DCP: des-γ-carboxyprothrombin, VN: vague nodular type, SN: simple nodular type, SNEG: simple nodular type with extranodular growth, CM: confluence multinodular type.

90.9%, and 78.6%, respectively, and the cumulative recurrence rates were estimated to be 16.8% at 1 year, 50.6% at 3 years and 62.8% at 5 years.

Risk factors for post-operative recurrence

To identify the risk factors for post-operative recurrence, the cumulative recurrence rates were compared for 18 clinically plausible factors (Table 2). Of these factors, the 11 items with $P < 0.20$ in the univariate analysis were selected as variables for inclusion in the multivariate regression analysis. The multivariate regression analysis using the Cox proportional hazard model with backward elimination identified the following six variables as independent risk factors for tumour recurrence: HCV infection, plasma DCP > 100 mAU/ml, the presence of underlying cirrhosis, the presence of microscopic vascular invasion, the presence of micrometastases and non-AR.

Comparison of anatomic and non-anatomic resections

The 1-, 3-, and 5-year survival rates were 99.4%, 92.2%, and 82.2% in the AR group, and 97.8%, 88.5%, and 71.9% in the non-AR group, respectively (P = 0.182) (Fig. 1). The 1-, 3- and 5-year recurrence rates were 16.6%, 44.6% and 56.7% in the AR group, and 17.2%, 61.9% and 74.7% in the non-AR group, respectively (P = 0.009). In the post-hoc analysis, the statistical powers to detect a difference of survival at 5 years and recurrence at 3 years at P = 0.05 were estimated as 52.6% and 74.8%, respectively.

A comparison of the patient characteristics between the AR and non-AR groups is shown in Table 3. Child–Pugh class B and liver cirrhosis were more prevalent, and the surgical margin tended to be smaller, in the non-AR group as compared with the AR group. However, when the groups were stratified by the width of the surgical margin (0 mm vs. >0 mm) and state of the background liver (cirrhosis vs. non-cirrhosis), a similar tendency, that is, of AR being superior to non-AR in respect of the tumour recurrence rate, was confirmed, regardless of the width of the surgical margin or state of the background liver.

Patterns of recurrence

The tumour recurrence patterns and initial treatments administered for recurrent lesions are summarized in Table 4. During the study period, recurrence was detected in 100 patients (54.3%) in the AR group and 65 patients (67.7%) in the non-AR group. The median time to recurrence was remarkably shorter in the non-AR group. Although the number and distribution of the recurrent nodules based on the segmental anatomy were similar between the two groups, local recurrence within the same portal segment was observed in 24 patients (25%) in the non-AR group, accounting for 37.5% of all tumour recurrences in this group. The interval from surgery to recurrence in the patients with local recurrence was significantly shorter as compared with that in the patients without local recurrence (13.2 months vs. 23.6 months, P = 0.001). Among the 24 patients with local recurrence, 19 patients developed the recurrence within 24 months after the surgery. When the patients with local recurrence were excluded, the cumulative recurrence curve of the non-AR group became similar to that of the AR group (Fig. 2).

Efficacy of anatomic resection

To clarify under what circumstances AR might be truly effective, the efficacy of AR was investigated according to the presence/absence of microscopic cancer spread[32] (i.e. microvascular invasion and/or micrometastases) and currently used size cut-off value for early HCC.[33,34] As shown in Fig. 3a–b, AR was superior only in patients with histopathologically proven microscopic cancer spread, and among the patients showing no histopatho-

Table 2 Risk factors of tumour recurrence

		n	Recurrence-free survival median (95% CI)	Univariate analysis			Multivariate analysis		
				P	HR	95% CI	*P*	HR	95% CI
Age	>65	136	38.7 (28.0–51.1)	0.992					
	≤65	144	32.4 (26.7–44.9)						
Gender	Male	210	35.6 (25.8–47.2)	0.966					
	Female	70	37.9 (25.8–50.0)						
HBsAg	+	59	41.0 (26.7–69.9)	0.251					
	–	221	34.3 (28.8–42.8)						
HCV-Ab	+	174	29.1 (24.0–37.9)	**0.003**	**1.64**	**1.18–2.30**	**0.001**	**1.79**	**1.27–2.52**
	–	106	55.5 (35.6–69.9)						
Child–Pugh	B	245	38.7 (28.9–50.4)	0.608					
	A	35	32.1 (24.0–37.9)						
Background liver	LC	129	50.4 (28.9–80.6)	**0.017**	**1.46**	**1.07–2.00**	**0.027**	**1.44**	**1.04–1.99**
	non LC	151	32.4 (24.7–38.9)						
Maximum diameter	>2 cm	202	35.6 (27.3–48.9)	0.195	1.25	0.98–1.80	0.631		
	≤2 cm	78	38.7 (28.8–64.7)						
Gross classification [a]	SNEG or CM	102	27.3 (21.0–48.3)	0.246					
	VN or SN	175	40.7 (32.4–55.5)						
Capsule formation	+	305	50.4 (33.3–69.4)	0.084	0.74	0.53–1.02	0.062		
	–	78	28.8)24.0–35.6)						
Differentiation	mod/por	54	29.9 (18.8–51.1)	0.433					
	Wel	219	37.9 (28.9–50.0)						
Microvascular invasion	+	60	28.8 (14.9–40.7)	**0.022**	**1.57**	**1.07–2.26**	**0.049**	**1.50**	**1.02–2.22**
	–	220	38.1 (30.0–55.5)						
Micrometastases	+	24	12.9 (6.6–25.8)	**0.004**	**2.24**	**1.33–3.57**	**0.004**	**2.09**	**1.26–3.46**
	–	256	38.1 (30.3–48.9)						
AFP (ng/ml)	>20	125	35.8 (32.1–40.7)	0.189	1.22	0.90–1.67	0.751		
	≤20	155	41.0 (32.1–59.4)						
DCP (mAu/ml)	>100	79	24.0 (16.9–58.1)	**0.037**	**1.44**	**1.02–2.00**	**0.007**	**1.64**	**1.14–2.36**
	<100	201	38.9 (30.3–50.0)						
Types of resection	Non-anatomic	96	28.8 (22.3–35.8)	**0.011**	**1.51**	**1.10–2.07**	**0.017**	**1.48**	**1.07–2.03**
	Anatomic	184	47.2 (30.4–64.4)						
Transfusion	+	7	37.9 (6.0–65.7)	0.630	1.29	0.40–3.05			
	–	259	35.9 (29.1–47.2)						
Tumour exposure [b]	+	65	25.5 (19.6–39.9)	0.012	1.57	1.11–2.20	0.200		
	–	215	38.1 (30.0–57.9)						
Surgical margin +1 mm				0.065	0.98	0.95–1.00	0.857		

Boldfaced entries represent significant factors in the final model.
[a]Classification of the Liver Cancer Study Group of Japan.[30]
[b]Exposure of the tumour capsule on the cut surface of the liver.
AFP, alfa-fetoprotein; DCP: des-gamma carboxyprothrombin; LC, liver cirrhosis; SNEG: simple nodular type with extranodular growth; CM, confluent multinodular type; VN, vague nodular type; SN, simple nodular type, wel/mod/por: well/moderately/poorly differentiated hepatocelluar carcinoma; HR, hazard ratio; 95% CI, 95% confidence interval.

logical evidence of microscopic tumour spread, there was no significant difference in the outcomes between the two surgical manoeuvres. Regarding the influence of the tumour size, AR was effective in HCC patients with tumours measuring 2 to 5 cm in diameter, whereas no significant difference in the tumour recurrence rate was observed between the two surgical manoeuvres in HCC patients with tumours measuring ≤2 cm in tumour diameter (Fig. 3c–d).

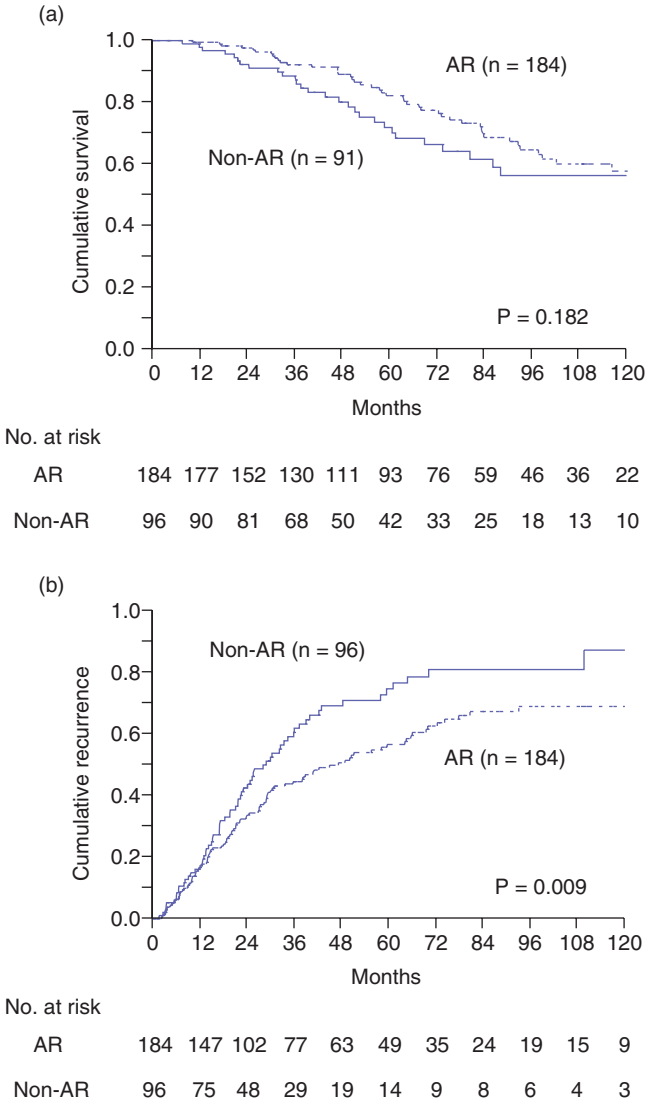

Figure 1 Long-term outcomes in patients treated by anatomic resection and non-anatomic resection. (a) overall survival; (b) recurrence rate. AR: anatomic resection; non-AR: non-anatomic resection

Discussion

In this study, the prognostic factors were analysed in patients with HCC having a solitary tumour measuring ≤5 cm in diameter who were treated by resection. The findings revealed that HCV infection, high plasma DCP levels, underlying cirrhosis, the presence of microvascular invasion and the presence of micrometastases were significant risk factors for post-operative recurrence of HCC. Also, anatomic resection was identified as the only modifiable factor to decrease the rate of recurrence. Comparison of the AR and non-AR groups revealed significantly higher recurrence rates in the non-AR group, although the difference in the overall survival between the two groups was not significant. The main clinicopathological differences between the two groups were the shorter time from surgery to recurrence and the higher local recurrence rate in the patients who had undergone non-AR. The prognostic advantage of AR was only observed in HCC patients with histopathologically proven microscopic cancer spread and in those with a solitary tumour measuring 2 to 5 cm in diameter.

Favourable outcomes of AR as the surgical strategy for HCC have been reported by several recent studies.[4,18,22–26,35] However, the oncological superiority of AR has been discussed mainly from the point of view of the long-term outcomes after surgery, and little clinicopathological evidence has been reported[23–25] to justify the adoption of AR as the preferred surgical resection strategy for HCC. Therefore, the current study focused on the difference in the pattern of recurrence and histopathological findings between the AR and non-AR groups, to clarify the clinicopathological bases for the prognostic difference between the two surgical strategies. Comparison of the AR and non-AR groups revealed that AR was superior to non-AR in terms of the tumour recurrence rate, independent of the width of the surgical margin (0 mm vs. >0 mm) or the histopathological characteristics of the background liver (cirrhosis vs. non-cirrhosis). Although the survival difference was not statistically significant, the 5-year survival rates exceeded 70% in both the groups, and post-hoc analysis revealed that the current population size was insufficient to show the survival difference with adequate statistical power in the background of such a high survival rate.

In the comparison to the mode of recurrence, no significant differences were observed in the size, number or distribution of the recurrent lesions. However, local recurrence within the same portal segment was observed in 25% of the patients after non-AR, and these patients were characterized by very early recurrence, with a median interval from surgery to recurrence of 13.2 months; these findings suggested that these recurrences had probably originated from undetectable residual micrometastases within the remaining part of the liver parenchyma. Interestingly, when the patients with local recurrence were excluded, the cumulative recurrence rate in the non-AR group became similar to that in the AR group. Furthermore a subset analysis revealed that AR was superior only in patients with histopathological evidence of microscopic cancer spread. These results suggest that the oncological superiority of AR was attributable to the reduced incidence of local recurrence associated with eradication of micrometastases within the tumour-bearing portal segment in AR. Similar results have been reported from recent studies that have explored the clinicopathological basis for the oncological advantage of AR.[23–25]

Regarding the width of the surgical margin, there was a significant difference between the AR and non-AR groups (median width, 5 mm vs. 1 mm). However, the difference was rather small and the rate of tumour exposure on the cut surface of the liver was relatively high in both the AR and non-AR groups. These observations may be attributable to the fact that extended resection beyond

Table 3 Comparison of clinicopathological characteristics between the patients with anatomic and non-anatomic resections

	Anatomic resection	Non anatomic resection	*P*
N	184	96	
Age, median (range)	66 (13–85)	64 (16–81)	0.404
Gender, male	138 (75.0)	72 (75.0)	1.000
HBsAg	43 (23.4)	16 (16.7)	0.192
HCV-Ab	112 (60.9)	62 (64.6)	0.543
Child–Pugh A/B	174 (94.6)/10 (5.4)	71 (74.0)/25 (26.0)	<0.001
Size (mm)	39 (8–50)	28 (8–50)	0.991
Macrostopic type[a]			
VN or SN	112 (60.5)	63 (65.6)	0.748
SNEG	45 (24.5)	20 (20.8)	
CM	23 (12.5)	13 (13.5)	
Others	4 (2.2)	0 (0)	
Histological grade			
Well	36 (20.0)	18 (19.4)	0.913
Moderate	129 (71.7)	65 (69.9)	
Poor	15 (8.3)	10 (10.8)	
Microvascular invasion	37 (20.1)	23 (24.0)	0.456
Micrometastases	11 (11.5)	13 (7.1)	0.213
Liver cirrhosis	91 (49.5)	60 (62.5)	0.037
Surgical time (min)	315 (260–374)	275 (211–340)	0.002
Blood loss (ml)	498 (314–776)	480 (213–821)	0.449
Inflow occlusion	169 (99.4)	81 (90.0)	<0.001
Transfusion	4 (2.3)	3 (3.4)	0.690
Surgical margin (mm)	1 (0–40)	5 (0–40)	<0.001
Tumour exposure [b]	27 (14.7)	38 (39.5)	<0.001
Specimen weight (g)	125 (5–920)	40 (1.5–260)	<0.001

Parentheses represent percentage unless indicated.
HBsAg: hepatitis B virus surface antigen, HCV-Ab: anti hepatitis C virus antibody.
[a]Classification of the Liver Cancer Study Group of Japan.[30]
[b]Exposure of the tumour capsule on the cut surface of the liver.
VN, vague nodular type; SN, simple nodular type; SNEG, simple nodular type with extranodular growth; CM, confluence multinodular type.

the segmental border is not always possible in patients with cirrhosis, as a result of the limited hepatic functional reserve. For example, when a tumour is attaching to the major hepatic veins or the inferior vena cava, extended resection or en-bloc resection of the veins is not always possible, especially in patients with a marginal hepatic functional reserve. In such cases, the tumour is carefully detached from the vein, while exercising special caution to avoid injury to the tumour capsule. Indeed, as shown by the results of the multivariate analysis, the tumour recurrence rate was not correlated with either exposure of the tumour capsule or the width of the surgical margin, as long as the capsule was not injured. In addition, a subset analysis revealed that AR was associated with a lower recurrence rate, regardless of the exposure of the tumour capsule on the cut surface of the liver. These results indicate that systematic removal of the tumour-bearing portal segments may be more important than securing a sufficient surgical margin to reduce the post-operative recurrence of HCC.

Recently, a retrospective study using a large cohort conducted by the Liver Cancer Study Group of Japan reported that AR may be effective in a specific group of HCC patients with tumours measuring 2 to 5 cm.[20] As shown in Fig. 3, similar results were obtained in the current study. AR was clearly effective in HCC patients bearing a solitary tumour measuring 2 to 5 cm, whereas among the patients with a maximum diameter of the tumour nodules of ≤2 cm, there was no significant difference in the post-operative recurrence rate between the AR and non-AR groups. Therefore, AR should be considered as the preferred surgical strategy, especially in HCC patients having a solitary tumour measur-

Table 4 Patterns of recurrence and treatment

	Anatomic resection (n = 184)	Non anatomic resection (n = 96)	P
Recurrence	100 (54.3)	65 (67.7)	
Time to recurrence (months) median (95% CI)	47.2 (30.4–64.4)	28.8 (22.3–35.8)	0.009
Number of recurrent nodules			
Median (range)	1 (1–20)	1 (1–20)	0.978
Solitary/multiple	57 (57.0)/43 (43.0)	39 (60.9)/25 (39.9)	0.617
Site of recurrence			
Intrahepatic	100 (100)	64 (98.5)	0.828
Same segment	NA	24/64 (37.5)	NA
Same sector	40/87 (46.0)	32/64 (50.0)	0.625
Adjacent sectors	64/100 (64.0)	44/64 (68.8)	0.531
Distant sectors	27/100 (27.0)	13/64 (20.3)	0.330
Extrahepatic	1 (1.0)	2 (3.1)	0.972
Treatment			
Surgery	56 (56.0%)	20 (30.8%)	0.014
RFA	12 (12.0%)	12 (18.5%)	
TACE/TAI	26 (26.0%)	31 (47.7%)	
Others	6 (6.0%)	2 (3.1%)	

95% CI, 95% confidence interval; SD, standard deviation; NA, not available.
Parentheses represent percentage. RFA: radiofrequency ablation, TACE: transarterial chemoembolization, TAI: transarterial infusion treatment.

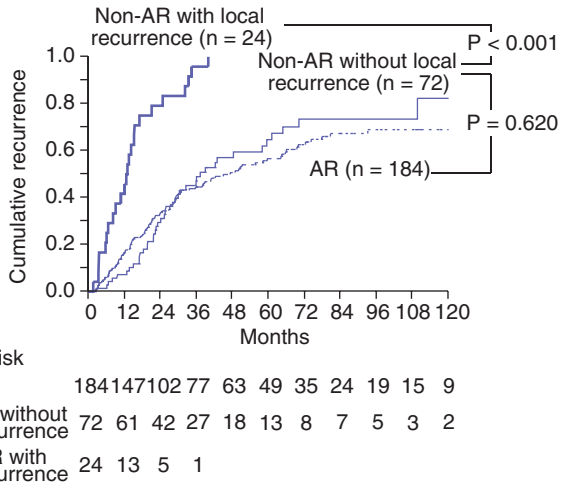

Figure 2 Comparison of the recurrence rate among patients with local recurrence after non-anatomic resection, patients without local recurrence after non-anatomic resection and patients treated by anatomic resection. AR: anatomic resection; non-AR: non-anatomic resection

ing 2 to 5 cm in diameter, as long as the hepatic functional reserve permits such a surgical manoeuvre.

The limitations of this study include its retrospective nature and imbalance of the patient population between the AR and non-AR groups. Because selection of the surgical manoeuvre was based on an algorithm that considered the hepatic functional reserve,[8] it is natural that patients in the non-AR group may have a lower mean hepatic functional reserve and higher incidence of cirrhosis. However, in our study, AR tended to be associated with a more favourable recurrence rate than non-AR, even after adjustments for the width of the surgical margin (0 mm vs. >0 mm) and the state of the underlying liver parenchyma (cirrhosis vs. non-cirrhosis). Also, the multivariate analysis revealed that the type of surgical manoeuvre was independently correlated with the tumour recurrence rate. Furthermore, based on the current analysis, the prognostic difference between the AR and non-AR group seemed to be explained mainly by the reduction of the local recurrence rate associated with eradication of undetectable residual micrometastases within the tumour-bearing portal segment in the AR group.

In conclusion, AR is the only modifiable factor that has been shown to have the potential to decrease the post-operative recurrence rate in patients with HCC. The oncological advantage of AR is related to its potential to eradicate micrometastases within the tumour-bearing portal segment, and up to 25% of patients may be expected to benefit from AR in terms of local recurrence. Based on the clinical results, AR is recommended for the initial resection of patients with HCC having a solitary tumour measuring 2 to 5 cm in diameter, as long as such extensive resection is permitted by the hepatic functional reserve.

Conflicts of interest

None declared.

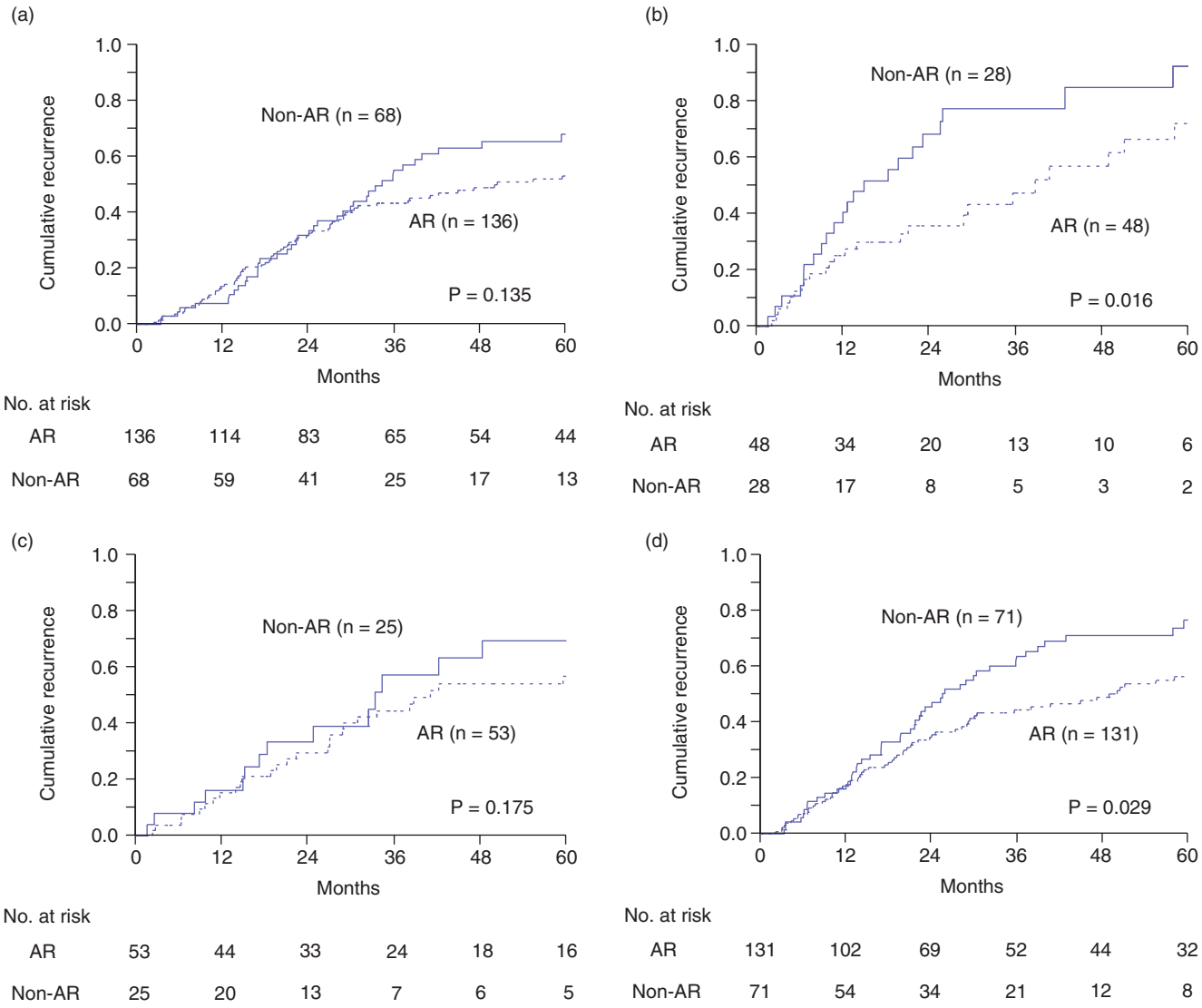

Figure 3 Comparison of the recurrence rates in subsets of the AR and non-AR groups. (a) microscopic cancer spread (-); (b) microscopic cancer spread (+); (c) hepatocellular carcinoma (HCC) measuring ≤2 cm in diameter; (d) HCC measuring 2 to 5 cm in diameter. AR: anatomic resection; non-AR: non-anatomic resection

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